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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : A61K 31/205		A1	(11) International Publication Number: WO 99/38505 (43) International Publication Date: 5 August 1999 (05.08.99)
(21) International Application Number: PCT/US99/01400			(81) Designated States: AL, AM, AT, AT (Utility model), AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, CZ (Utility model), DE, DE (Utility model), DK, DK (Utility model), EE, EE (Utility model), ES, FI, FI (Utility model), GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SK (Utility model), SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).
(22) International Filing Date: 22 January 1999 (22.01.99)			
(30) Priority Data: 09/016,254 30 January 1998 (30.01.98) US			
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(54) Title: COMPOSITIONS FOR PREVENTION AND TREATMENT OF COLD AND INFLUENZA-LIKE SYMPTOMS ASSOCIATED WITH RESPIRATORY TRACT INFECTIONS			
(57) Abstract			<p>The present invention is a composition for prevention and treatment of cold and influenza-like symptoms associated with respiratory tract infections. Also included herein are the methods of use of such compositions.</p>

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COMPOSITIONS FOR PREVENTION AND TREATMENT
OF COLD AND INFLUENZA-LIKE SYMPTOMS ASSOCIATED WITH
RESPIRATORY TRACT INFECTIONS

5

FIELD OF USE

10 The present invention is for compositions and their methods for prevention and treatment of cold and influenza-like symptoms due to respiratory tract infections. These compounds and their method of application are effective in both preventing the onset of the symptoms of colds and influenza or significantly mitigating them if already afflicted with such symptoms.

15 BACKGROUND SUMMARY OF THE ART

It is known that many different viruses and viral strains bring on symptoms associated with respiratory viral infections. Pinpointing the specific cause of the illness is difficult and not practical since there are also a number of predisposing factors whose contribution to the manifestation of symptoms is not fully understood.

20 Such include, but, are not limited to physical fatigue, psychological stress, and overall physical healthiness.

Regardless of the virus and associated factors leading to the onset of cold and influenza symptoms, a number of remedies to alleviate the symptoms of the common cold have been suggested. The cough/cold products that are currently marketed typically contain one or more of the following actives: nasal decongestants such as pseudoephedrine, oxymetazoline, antihistamines such as doxylamine, antitussives such as dextromethorphan, expectorants such as guaifenesin and anti-pyretics such as acetaminophen. In an attempt to improve existing cold remedies, experts in the field have suggested several alternative pharmacotherapies and subsequently conducted cold trials to test their efficacy. Examples of these therapies include the use of interferon- α_2 , see Douglas et al., Prophylactic Efficacy of Intranasal Alpha₂- Interferon Against Rhinovirus Infection in the Family Setting, The New England Journal of Medicine, 314, pp. 65-70, 1986; bradykinin antagonist, see Higgins et al., A Study of the Efficacy of the Brandykinin Antagonist, NPC567,

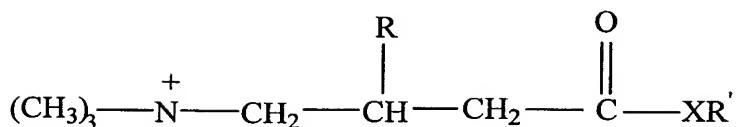
in Rhinovirus Infections in Human Volunteers, Antiviral Research vol. 14, pp. 339-344, 1990; glucocorticoid, see Farr et al., A Randomized Controlled Trial of Glucocorticoid Prophylaxis Against Experimental Rhinovirus Infection, The Journal of Infectious Diseases vol. 162, pp. 1173-1177, 1990; nedocromil, see Barrow et al.,
5 The Effect of Intranasal Nedocromil Sodium on Viral Upper Respiratory Tract Infections in Human Volunteers, Clinical and Experimental Allergy vol. 20, pp. 45-51, 1990; a combination of interferon- α_2 , ipratropium and naproxen see Gwaltney, Combined Antiviral and Antimediator Treatment of Rhinovirus Colds, The Journal of Infectious Diseases vol. 166, pp. 776-782, 1992; zinc salts see Potter et al., DIAS
10 Rounds, Zinc Lozenges for Treatment of Common Colds, The Annals of Pharmacotherapy vol. 27, pp. 589-592, 1993.

A number of patents have also been issued disclosing compositions for prevention and treatment of the common cold and their methods of use. A sample of such patents include: US Patents 5,240,694; 5,422,097; and 5,492,689; all to
15 Gwaltney, disclosing treatment using combinations of anti-viral and anti-inflammatory compounds; US Patents Re 33,465 and 5,409,905; both to Eby disclosing treatment using zinc salts; US Pat. 5,626,831; to Van Moerkerken disclosing treatments using orally administered aminocarboxylic acid compounds; U.S. Patents 4,619,934 and 4,552,899, both to Sunshine, disclosing treatment of
20 cough and colds using compositions comprising non-steroidal anti-inflammatory drugs such as NSAIDS with antihistaminically effective materials such as chlorpheniramine.

Despite the abundance of compositions and preventative treatments known in the art, there remains a need to provide a consistent and effective method for
25 prevention and treatment of cold and influenza symptoms.

SUMMARY OF THE INVENTION

The present invention is for respiratory tract compositions and methods for using such compositions for prevention and treatment of cold and influenza-like symptoms due to respiratory tract infections. These methods include the
30 administration of an respiratory tract composition comprising compounds conforming to the following chemical structure:



DEFINITIONS

The following are the definitions that should be applied to the terms used to.

5 describe the present invention:

“Respiratory tract compositions” refers to compositions in a form that is directly deliverable to the airway passages from the nose and mouth. These compositions include, but are not limited to droppers, pump sprayers, pressurized sprayers, atomizers, air inhalation devices and other packaging and equipment

10 known or yet to be developed.

“Cold and influenza-like symptoms” refers to symptoms typically associated with respiratory tract viral infections. These symptoms include, but not limited to nasal congestion, chest congestion, sneezing, rhinorrhea, fatigue or malaise, coughing, fever, chills, body ache, sore throat and headache and other known cold

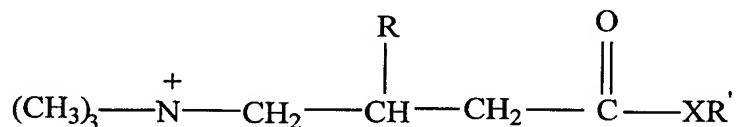
15 and influenza-like symptoms.

“Pharmaceutically acceptable vehicle” refers to any solid, liquid or gas combined with compound in the composition of the present invention to deliver the compound to the respiratory tract of the user. These vehicles are generally regarded as safe for use in humans.

20 **DETAILED DISCUSSION OF THE INVENTION**

The present invention is for respiratory tract compositions and the methods of using said compositions for preventing or treating the cold and influenza-like symptoms associated with respiratory tract infections. The method provides for administering a composition into the respiratory tract comprising compounds

25 conforming to the following chemical structure:



wherein R is selected from the group consisting hydrogen (-H); hydroxyl group (OH); ester groups having the structure -OCOR'' wherein R'' is selected from the group consisting of C₁ to C₁₈ branched and straight chained alkyl groups, non-
5 substituted aryl groups, aryl groups substituted with chlorine (-Cl), fluorine (-F) bromine (-Br), a hydroxyl group (-OH), a carboxyl group (-COOH), groups having the structure -OR''' and -COOR''' wherein R''' is selected from the group consisting of branched and straight chained alkyl groups having from 1 to about 4 carbon atoms; X is selected from the group consisting of oxygen (-O) and nitrogen (-N); and
10 R' is selected from the group consisting of hydrogen (-H); two hydrogen atoms (-H₂); and R''.

These compounds can also be in the form of a free base or salt. Examples of such salts include but not limited to those formed by addition of maleic acid, hydrogen chloride, hydrogen bromide, EDTA, tartaric acid and mixtures thereof.

15 Preferred compounds used in the present invention include the above structures wherein R is selected from the group consisting of -OH, -OCOR'' and -H, X is -O and R' is selected from the group consisting of -H, and R''. Most preferred is where R is -OH, X is -O and R' is -H. Such a preferred compound is 3-carboxy-2-hydroxy-N,N,N-trimethyl-1-propanaminium hydroxide, inner salt; see Merck
20 Index, 10th Ed., 1983, at p. 257. Said compound is also known in the art as L-carnitine or levocarnitine. L-carnitine is commercially available from Lonza Ltd. Basel, Switzerland.

The use of L-carnitine is known in the art for acute treatment of patients with an inborn error of metabolism that results in secondary carnitine deficiency, primary
25 systemic carnitine deficiency and dietary supplement for renal patients; see Physicians Desk Reference, pp. 2623 to 2624, and 2767 to 2768, 1997. L-carnitine is also known for use in commercially available products marketed as dieting aids, special diet foods and meal replacements, sports aids and general nutritional support. Typically it is found as one of the ingredients in a multi-component product in the
30 solid or liquid form (tablets, capsules, tonics, beverages) to be ingested orally.

The inner salt of 3-carboxy-2-hydroxy-N,N,N-trimethyl-1-propanaminium hydroxide or L-carnitine may be structurally modified to yield esters. Synthetic reactions for producing such esters are those that are routinely practiced one skilled in the chemical arts. Examples of reagents and synthetic techniques useful for 5 making such esters are found in a number of references including Fieser, Reagents for Organic Synthesis, p. 1309, 1967; Furuta, Gao, Yamamoto, Organic Synthesis, pp. 72, 86, 1993; and Bremer, Biochemical Preparation, Vol.12, p. 69, 1968. These L-carnitine inner salt esters have carboxyl groups esterified with a compound selected from the group consisting of alpha, beta, gamma and delta tocopherol; 1,2- 10 dimethyl-3-hydroxypyrid-4-one; (S)(-)6-hydroxy-2,5,7,8-tetramethylchroman-2- carboxylic acid or mixture of (S)(-) and (R)(+)6-hydroxy-2,5,7,8- tetramethylchroman-2-carboxylic acid. Other L-carnitine esters useful in the present invention include those having the hydroxyl group of the above compound esterified 15 with ascorbic acid, (S)(-)6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid or mixture of (S)(-) and (R)(+)6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid. The 6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid is available as “Trolox” from Aldrich Chemical Company. These later types of esters can be further esterified at the carboxyl group with R''. The absolute configuration and enantiomer designation of these compounds are defined using the established 20 terminology “S and R” and “+ and -”, respectively, see Dean, Handbook of Organic Chemistry, pp. 1-48, 1-51, 1987.

The level of the above-described compounds varies with its compositional form. For example, when the compositional form is a liquid, the level of the compound ranges from about 0.01% to about 50%, preferably from about 0.05% to 25 about 20% and most preferably from about 0.1% to about 5% of the composition. Where the compositional form is a powder, the level of the compound in said composition ranges from about 0.01% to 100%, preferably from about 0.1% to about 99% and most preferably from about 20% to about 90% of the composition.

Depending on the desired form and delivery device to be used, compositions 30 of the present invention may include a pharmaceutical acceptable vehicle. Pharmaceutically acceptable vehicles for liquid forms of the composition of the

present invention include aqueous buffered solutions or dispersions; aqueous buffered solutions or dispersions containing co-solvents such as ethanol, propylene glycol, water-miscible solvent; liquid aerosol propellants and mixtures thereof. Preferably these vehicles have an osmotic pressure that is about equal to that of 5 human plasma and a pH approximately that of typical nasal secretions for use in intranasal products or the environment of the lungs for use in inhalation products. The vehicle may also contain buffers for pH stability, preservatives to prevent inoculating dosing devices inserted into the nose with microorganisms. Volatile oils, sensates and flavors may also be included to provide desirable in-use smell and 10 taste of the composition. The vehicle may also contain surfactants to aid in spreading the composition throughout the respiratory tract. Gums, mucilages, thickeners, mucoadhesive polymers and mixtures thereof may be included in order to slow the normal physiologic clearance of the solution from the nasal cavity to the oropharynx. Where the composition of the present invention is in the form of a 15 liquid, the vehicle is used in a level from about 50% to about 99.99%, preferably from about 80% to about 99.95% and most preferably from about 95% to about 99.9% of the treatment composition.

Where the composition of the present invention is a solid form the vehicle may be applied in a powder form without use of a specific vehicle. However, 20 vehicles are often added to aid in processing of the compounds, providing acceptable flowability and particle size for inhalant application. Other particulate or powdered pharmaceutically acceptable filler materials may be combined with compounds of the present invention to facilitate flowability, stability, handling, hygroscopicity; favorable flavor, taste and, or sensation. In the present invention, the solid vehicle is 25 from 0% to about 99.99%, preferably from about 1% to about 99.9% and most preferably from about 10% to about 80% of the composition.

EXAMPLES

The following are non-limiting examples of compositions of the present invention. All ingredients are by weight of 100 grams of the composition:

5

Example: 1 Intranasal spray solution

1.00 grams L-carnitine free base
0.70 grams nonionic detergent ¹
0.11 grams dibasic sodium phosphate
10 0.38 grams monobasis potassium phosphate
0.04 grams benzalkonium chloride
0.26 grams chlorhexidine gluconate
0.01 grams disodium EDTA
flavoring ²
15 camphor and eucalyptol ³
purified water QS to 100 grams

1 Available as Tyloxbapol from Nycomed, Inc.

2 Flavoring used at a level in order to provide a pleasing taste.

3 Added at a level in order to provide a pleasant in-use scent.

20 Add all ingredients to chilled water and stir until dissolved , while maintaining the chill water temperature. Adjust this solution to pH of 5.5 to 6.5. QS with water and filter through a cellulose acetate membrane filter. Fill manually operated nasal sprayers with the composition. Spray from about 5 to 500 microliters of solution into each nostril. Repeat three times daily.

25

Example 2: Intranasal drops:

0.115 grams methylcellulose gum
0.350 grams sodium chloride
0.540 grams monobasic potassium phosphate
30 0.310 grams dibasic potassium phosphate
0.145 grams poloxamer block co-polymer ¹

1.170 grams propylene glycol
0.568 grams L-carnitine hydrochloride
0.025 grams benzalkonium chloride
flavoring ²
5 camphor and eucalyptol ³
purified water QS to 100 grams

1 Available as Pluronic 127 from BASF Corporation.

2 Flavoring used at a level in order to provide a pleasing taste.

3 Added at a level in order to provide a pleasant in-use scent.

10 Add all ingredients except methylcelullose to chilled water and stir until dissolved , while maintaining the chill water temperature. Adjust this solution to pH of 6.5 - 7.0 , QS with water and filter through a cellulose acetate membrane filter. Add the methylcellulose to the chilled solution and stir under refrigeration to hydrate. Fill dropper vials with the solution and cap. Apply one drop of the solution
15 to each nostril with the head tilted upward. The head is held briefly in this position to permit spreading of the solution over the nasal turbinates. Repeat 3 times daily.

Example 3: Intranasal powder:

5.0 grams acetyl L-carnitine
20 5.0 grams dextrose powder
1.0 gram ethanol
flavoring ¹
camphor and eucalyptol ²
lactose powder QS to 100 grams.

25 1 flavoring is used in an appropriate amount to provide a pleasing taste.

2 added at an appropriate level to provide a pleasant in use scent.

Mix acetyl L-carnitine with the dextrates in a V-mixer. Micronize this mixture in a fluid energy mill at 100 pounds per square inch dry air pressure. Mix the micronized material by geometric addition with the lactose in a V-mixer.

30 Dissolve camphor, eucalyptol, and flavors in ethanol, spray coating the powder with the liquid in a V-mixer. Evaporate the ethanol after mixing by pan drying. Fill dry

powder nasal inhalation metering pumps with the powder. Such pumps include Prohaler DPI from Valois Corporation. Apply ten milligrams of the powder to each nostril while inhaling. Repeat three times daily.

5 Example 4: Inhalant:

0.60 grams acetyl L-carnitine

0.40 grams sorbitan trioleate

49.50 grams propellant 114¹

49.51 grams propellant².

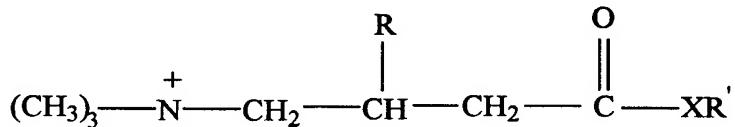
10 1 Freeon 114 E.I. Dupont

2 Freeon 12 E.I. Dupont.

Micronize the acetyl L-carnitine in a fluid energy mill at 100 pounds per square inch pressure. Dissolve the sorbitan trioleate in the mixed propellants. Disperse the acetyl L-carnitine in the sorbitan trioleate / propellant liquid. Fill the 15 suspension in to the canister of a pressurized metered dose inhaler using standard filling techniques. Administer 100 to 200 microliters from the metered dose inhaler into the mouth, while inhaling.

WHAT IS CLAIMED IS:

1. An respiratory tract composition for prevention and treatment of cold and influenza-like symptoms due to respiratory tract infections wherein said composition comprising a compound conforming to the following structure:



wherein R is selected from the group consisting hydrogen (-H); hydroxyl group (OH); ester groups having the structure -OCOR'' wherein R'' is selected from the group consisting of C₁ to C₁₈ branched and straight chained alkyl groups, non-substituted aryl groups, aryl groups substituted with chlorine (-Cl), fluorine (-F) bromine (-Br), a hydroxyl group (-OH), a carboxyl group (-COOH), groups having the structure -OR''' and -COOR''' wherein R''' is selected from the group consisting of branched and straight chained alkyl groups having from 1 to 4 carbon atoms; X is selected from the group consisting of oxygen (-O) and nitrogen (-N); and R' is selected from the group consisting of hydrogen (-H); two hydrogen atoms (-H₂); and R'';

X is selected from the group consisting of oxygen (-O) and nitrogen (-N); and R' is selected from the group consisting of hydrogen (-H); two hydrogen atoms (H₂) and R''.

2. The composition according to Claim 1 wherein said compound comprises from 0.01% to 100% of said compound.
3. The composition according to Claim 2 wherein said compound conforms to the structure where R is selected from the group consisting of -OH, -OCOR'' and -H, X is -O and R' is selected from the group consisting of -H, and R''.

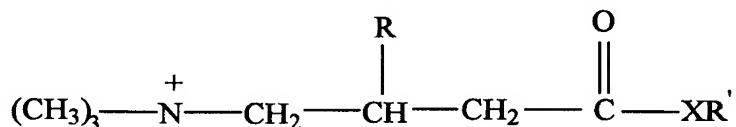
4. The composition according to Claim 3 wherein said compound conforms to the structure where R is -OH, X is -O and R' is -H.

5. The composition according to Claim 4 wherein the compound is 3-carboxy-2-hydroxy-N,N,N-trimethyl-1-propanaminium hydroxide inner salt.

6. A liquid composition according to Claim 5 comprising from 0.01% to 50% of said compound.

7. The composition according to claim 6 additionally comprising from 50% to 99.99% of a pharmaceutically acceptable vehicle.

8. A process for making compositions comprising a compound conforming to the following structure:



wherein R is selected from the group consisting hydrogen (-H); hydroxyl group (OH); ester groups having the structure -OCOR'' wherein R'' is selected from the group consisting of C₁ to C₁₈ branched and straight chained alkyl groups, non-substituted aryl groups, aryl groups substituted with chlorine (-Cl), fluorine (-F) bromine (-Br), a hydroxyl group (-OH), a carboxyl group (-COOH), groups having the structure -OR''' and -COOR''' wherein R''' is selected from the group consisting of branched and straight chained alkyl groups having from 1 to 4 carbon atoms; X is selected from the group consisting of oxygen (-O) and nitrogen (-N); and R' is selected from the group consisting of hydrogen (-H); two hydrogen atoms (-H₂); and R''; X is selected from the group consisting of oxygen or -O and nitrogen or -N; and R' is selected from the group consisting of hydrogen; two hydrogen atoms and R'' wherein said composition is used for prevention and treatment of cold and influenza-like symptoms due to respiratory tract infections.

9. The process according to Claim 8 wherein the composition is administered to the respiratory tract, wherein said compound of said composition conforms to the structure where R is selected from the group consisting of -OH, -OCOR'' and -H, X is -O and R' is selected from the group consisting of -H, and R''

10. The process of Claim 9 wherein said compound conforms to the structure where R is -OH, X is -O and R' is -H.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 99/01400

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 A61K31/205

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 626 831 A (VAN MOERKERKEN ARTHUR) 6 May 1997 see page 4, Table I, compound 7 see column 7, line 29 - line 42 ---	1-4,6-10
X	EP 0 681 839 A (KURATSUNE HIROHIKO ;KITANI TERUO (JP)) 15 November 1995 see column 5, line 12 - line 13 see column 5, line 25 - line 26 see column 7, line 17 - line 19 see column 7, line 35 - line 39 ---	1-3,6-9
X	WO 89 11276 A (BERNARDINI ATTILIO) 30 November 1989 see page 3, line 1 - line 3 see page 4, line 9 see page 15, line 1 - line 4 ---	1-3,8,9



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 99/01400

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>DAL NEGRO ET AL: "L-carnitine and rehabilitative respiratory physiokinesthesia: metabolic and ventilatory response in chronic respiratory insufficiency" INT J OF CLIN PARMACOL, THERAP AND TOXICOL, vol. 24, no. 8, 1986, pages 453-456, XP002103369 see abstract</p> <p>---</p>	1,3,4, 8-10
X	<p>BE 660 039 A (STÉ BELGE DE L'AZOTE ET DES PRODUITS CHIMIQUES DU MARLY) 23 August 1965 see page 1, line 3 - line 11</p> <p>-----</p>	1,8

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 99/01400

Patent document cited in search report	Publication date	Patent family member(s)			Publication date
US 5626831 A	06-05-1997	AU 7605996 A	15-05-1997		
		CA 2235746 A	01-05-1997		
		EP 0866694 A	30-09-1998		
		WO 9715299 A	01-05-1997		
EP 0681839 A	15-11-1995	JP 8026987 A	30-01-1996		
		US 5576348 A	19-11-1996		
WO 8911276 A	30-11-1989	CH 676930 A	28-03-1991		
		AT 81454 T	15-10-1992		
		AU 3579189 A	12-12-1989		
		EP 0403575 A	27-12-1990		
		JP 3500656 T	14-02-1991		
		US 5314689 A	24-05-1994		
BE 660039 A	23-08-1965	CH 458320 A			
		DE 1242222 B			
		FR 1466696 A	07-04-1967		
		GB 1075563 A			
		NL 6601978 A	23-08-1966		